63. (Amended) A kit comprising one or more unit dosage containers containing a pharmaceutical composition, each unit dosage container containing a pharmaceutical composition comprising:

(a) a tiotropium salt; and

(b) a steroid,

each optionally together with a pharmaceutically acceptable excipient.

64. (Original) The kit according to claim 63, further comprising instructions with directions for using the kit.

65. (Amended) A kit comprising:

(a) a first container containing a first pharmaceutical formulation comprising a tiotropium salt; and

(b) a second container containing a second pharmaceutical formulation comprising a steroid,

each container each optionally further containing a pharmaceutically acceptable excipient.

66. (Original) The kit according to claim 65, further comprising instructions with directions for using the kit.

REMARKS

Claims 59-60 are held to be drawn to a nonelected invention, without traverse, and must be cancelled in the response to the final rejection. Claims 59-60 are, accordingly, cancelled, without prejudice, to permit applicant the right and opportunity to prosecute the subject matter of those claims in applications claiming the benefit hereof.

Claims 3-4, 7-8, 10, 16-17, 25-26, 28, 30, 32 and 36-37 are objected to as being directly or indirectly dependent from canceled claim 2. Those claims now derive, directly or indirectly, from claim 1, and that objection should be reconsidered and withdrawn.

Claims 39 and 63-66 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Nishimura et al. in view of Banholzer. Although conceding that "Nishimura et al. does

not teach tiotropium salts as anticholinergic agents, useful in asthma treating compositions...[and] Neither does it teach a kit.", it is, nevertheless, contended that it would have been obvious to employ the tiotropium bromide of Banholzer et al. (5,610,163) in lieu of the ipratropium bromide or oxitropium bromide of Nishimura to make a kit to treat asthma. It is further proposed that "the incorporation of a pharmaceutical composition into a kit with a set of instructions is within the purview of the skilled artisan and is therefore obvious."

Applicants respectfully traverse those rejections.

Claims 1, 3-5, 7-10, 15-23 and 25-28 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Nishimura et al. in view of Banholzer et al. ('163 patent) and further in view of Gennaro et al. Although conceding that neither Nishimura et al. nor Banholzer et al. ('163 patent) teach the employment of the specific excipients, co-solvents or particle sizes recited in the claims, Gennaro et al. provides the teaching of excipients and pharmaceutical necessities for inhalers, along with particle sizes to make it obvious to employ the specific excipients and particle sizes herein absent a showing of criticality.

Applicants also respectfully traverse the rejections under Section 103 set forth above.

Applicants' invention relates to the discovery of novel compositions comprising the combination of anticholinergics and corticosteroids and their use to treat respiratory diseases. More particularly, the claimed invention relates to the discovery of beneficial composition for treating respiratory diseases comprising tiotropium salt, a steroid, and a saccharide, preferably a mono- and/or disaccharide. It has been discovered, unexpectedly, that, administration of a composition comprising a steroid and a tiotropium salt produces a beneficial effect in the treatment of inflammatory or obstructive diseases.

Nishimura et al. refers to the results of a study of inhaled oxitropium bromide in combination with inhaled beclomethasone in the treatment of elderly asthmatic patients. Nishimura et al. concedes that "[a]lthough significant improvement was observed [against placebo] in the present study, the magnitude of the improvement appears to be rather small [p. 87, col. 2]. Nishimura et al., not satisfied wit the results of his combination treatment, recommends further testing with combinations of "sustained-release theophylline, long-acting B_2 receptor agonists and anti-cholinergics" on patients whose asthma is not adequately

controlled by beclomethasone. Nishimura does not provide guidance or preference toward the use of any one class of drugs, or combination of drugs, over another in the future studies for the treatment of asthma.

Banholzer refers to "novel thienylcarboxylates of amino alcohols and their quaternary products", including tiotropium salts, useful to treat asthma when administered by inhalation.

Gennaro et al. (Remington's) is a general compendium of pharmaceutical sciences and refers, rather comprehensively, to the possible use of various pharmaceutical additives and generally useful particle sizes for pharmaceutical compositions.

At the outset, not all chemical agents having anti-cholinergic activity would be suitable agents to treat respiratory disease. That is, compounds found to exert a reduction of parasympathetic nerve impulses or the selective inhibition of muscarinic (M1-M5) or nicotinic mechanisms, affect a variety of physiologic functions, most notably, in depression and Parkinson's disease (e.g., atropine). Thus, there can be no presumption of a common class effect among anti-cholinergics in the treatment of respiratory disease. More specifically, the pharmacology of tiotropium (slow onset and offset due to prolonged M3 receptor dissociation in the treatment of respiratory diseases) cannot be predicted from the effects of non-selective binding of ipratropium or oxitropium, particularly, when administered in combination with another active ingredient.

Most importantly, the cited art simply fails to disclose or suggest the use of tiotropium salt with any other active ingredient in the treatment of respiratory disease. Moreover, the physico-chemical interaction between tiotropium salts and corticosteroids and their physiologic effects cannot be predicted based on the disclosure of Nishimura et al. Thus, incorporation of the composition into a kit cannot be rendered obvious.

Moreover, the generic disclosure of all available excipients for producing inhalation powders does not necessarily lead the ordinarily skilled worker to saccharides as excipients useful to provide tiotropium with the beneficial therapeutic distribution characteristics of the claimed clinical combination in the lung.

Given the cited art, it is not obvious that tiotropium salt could be mixed with a steroid and a saccharide excipient to produce a desirable pharmacologic effect in respiratory disease, and not be burdened by biologic or chemical interaction, pharmacologic inhibition, or produce an unacceptable toxicity. Before applicants' invention, it was unknown, and unknowable, whether administration of the claimed composition to a patient would adversely impact the patient, for example, producing unacceptable pulmonary absorption resulting in therapeutic failure or harm.

At most, "An 'obvious-to-try' situation exists when a general disclosure may pique the scientist's curiousity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." In re Eli Lilly & Co., 902, F.2d 943, 945, 14 USPQ 2d 1741, 1743 (Fed. Cir. 1990)].

In light of the above arguments and remarks, applicants respectfully submit that the pending claims are in condition for allowance.

Early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

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